A Phase II Randomized Study of GM-CSF Gene-Modified Autologous Tumor Vaccine (CG8123) with and without Low-Dose Cyclophosphamide in Advanced Stage Non-Small Cell Lung Cancer
Scientific Abstract

Background

There are approximately 170,000 new cases of lung cancer in the United States each year and almost 160,000 annual deaths. Lung cancer remains the leading cause of cancer-related mortality in both men and women in North America. Although early stage disease is curable in some patients following complete surgical resection, more than two-thirds of patients present with advanced stage disease that is fatal in > 90% of patients despite existing therapies. Approximately 75% of lung cancer cases are made up of non-small cell lung cancer (NSCLC) histologies, including adenocarcinoma, squamous cell carcinoma, large cell, bronchioloalveolar, and other. Of these, the most common subtypes are adenocarcinoma and squamous cell. By far the greatest risk factor for lung carcinogenesis is tobacco exposure.

Combination cisplatin-based chemotherapy of NSCLC has been shown to prolong survival, improve quality of life, and decrease health care costs, compared with supportive care alone, but the absolute benefits are small (improvement in median survival by approximately 2-3 months) and such therapy is associated with significant toxicities. Docetaxel is the only FDA-approved agent for good performance status patients with advanced stage NSCLC who have failed at least one prior platinum-containing regimen. Nevertheless, the toxicities of docetaxel are substantial and the absolute benefit modest. Clearly, there is still an unmet medical need for new therapies that demonstrate efficacy in NSCLC with less associated toxicity than chemotherapy.

Therapeutic cancer vaccines represent a novel treatment strategy for NSCLC with a goal of inducing tumor-specific immune responses and reversing pre-existing immune tolerance to endogenous tumors. We have developed a cancer vaccine based on genetic modification of autologous tumor cells with an adenoviral vector containing the gene for human granulocyte-macrophage colony stimulating factor (GVAX®). Preclinical studies with such vaccines have demonstrated induction of potent anti-tumor immunity. Two Phase I/II studies of this GVAX® platform (CG7773) in early and advanced stage NSCLC have demonstrated encouraging results. Both trials confirmed the feasibility and safety of this vaccine approach and demonstrated preliminary evidence of clinical activity including induction of tumor-associated immune responses as well as radiologic tumor regressions. In the first trial, 1 of 33 treated patients had a mixed tumor response. Two additional patients who underwent resection of all visible metastatic sites for vaccine generation have remained without evidence of recurrent disease for over three years. In the second trial, 3 of 33 patients with advanced stage disease who received vaccine treatment achieved durable, complete tumor regressions and 3 additional patients had mixed or minor tumor responses. In both trials, the vaccine was well tolerated with the most common vaccine-related adverse event being grade 1/2 injection site reactions in

>90% of patients. Less common systemic toxicities considered possibly vaccine-related experienced by > 5% of patients included asthenia, pain, fever, rhinitis, weight loss, myalgia, infection, nausea, and fatigue. Serious adverse events reported as possibly related to vaccine treatment included pneumonia, pericardial effusion, dehydration, and fever.

A new study has been initiated that will evaluate an updated version of the CG7773 vaccine product tested in the two previous trials, termed CG8123. CG8123 incorporates several modifications from the previously tested CG7773 vaccine product including, 1) use of a more efficient adenoviral GM-CSF vector (CG6444), 2) use of a modified closed-system manufacturing process, 3) elimination of bovine products from the process, and 4) cryopreservation at -70°C rather than liquid nitrogen.

Objectives

The primary objective of this study is to assess the impact of co-administration of immunomodulatory doses of cyclophosphamide on vaccine efficacy. It has long been hypothesized that patients with cancer develop peripheral tolerance to their tumor. It has previously been reported that immune-modulating doses of cyclophosphamide enhance vaccine-induced anti-tumor immune responses by inhibiting suppressor T-cell activity in animal models. Several clinical trials have also demonstrated enhanced immune responses and possible improvement in survival following treatment with low-dose cyclophosphamide with cancer vaccines compared with vaccine treatment alone. Secondary objectives include assessment of manufacturing feasibility, safety, quality of life, disease progression, and survival.

Patient Population

Stage IIIB/IV NSCLC, with accessible tumor to harvest for vaccine processing using a minor surgical procedure, measurable tumor remaining following tumor harvest, and ECOG 0-2. 100 patients will undergo tumor procurement and it is estimated that ~ 60 will proceed to randomization and study treatment. Approximately 40% of patients are predicted to drop out prior to vaccine treatment due to manufacturing failures (~ 20%) and disease progression (~ 20%).

Study Design

Phase II multi-center, open-label, randomized study. Patients will be randomized at a ratio of 1:1 into one of two treatment groups: CG8123 only (Cohort A) and CG8123 plus a single dose of cyclophosphamide (250mg/m^2 IV) at Day -1 for vaccine cycles 1, 3, and 5 (Cohort B). Randomization will occur following successful release of vaccine product (approximately one month following tumor harvest).

Dose and Schedule

Patients will receive intradermal (ID) vaccine injections every two weeks for up to five vaccine cycles. Vaccine dose will be individualized for each patient based on vaccine yield

and will range from 2 x 10^6 -300 x 10^6 tumor cells/vaccination. The dose for each vaccine will be the same. Cyclophosphamide will be administered as described above in Cohort B only.

Endpoints

Vaccine manufacturing feasibility will be monitored by evaluation of vaccine cell yield, viability, GM-CSF secretion, sterility, and overall manufacturing success rate. Immunologic response to vaccination will be monitored by assessment of vaccine injection site reactions, delayed-type hypersensitivity (DTH) skin testing to injections of autologous tumor cells, and induction of new tumor-reactive antibodies post vaccination. Safety will be monitored by physical examination, laboratory evaluations, and assessment of adverse events. Tumor response will be followed by radiologic evaluations. Patients will also be monitored for progression-free survival and overall survival. Quality of life assessments will be performed to measure improvements in cancer-related symptoms.

Product

Patient tumor tissue collected at clinical sites will be shipped to a central Cell Genesys facility for vaccine production. Solid tumors are digested to a single-cell suspension using mechanical methods. Tumor cells from pleural effusions are isolated using density gradient separation. Tumor cells are then genetically modified to secrete human GM-CSF by exposure to a replication-deficient adenoviral vector containing the gene for human GM-CSF (CG6444). Following transduction, cells are washed and irradiated to prevent cell proliferation. Cells are then aliquoted into vials and frozen at -70°C until immediately prior to administration.

Status

This study is currently open for enrollment.